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RING BROMINATION IN THE ATTEMPTED NITRATION OF 2,5-DIBROMO-3-DIBROMOMETHYLTHIOPHEN

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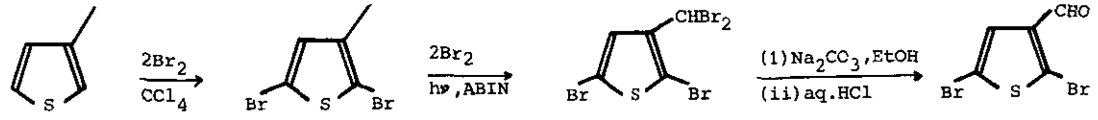
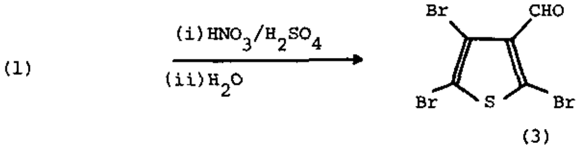
Abstract - Treatment of 2,5-dibromo-3-dibromomethylthiophen with mixed nitric and sulphuric acids or with fuming (>96%) nitric acid gives 2,4,5-tribromothiophen-3-carbaldehyde after aqueous work-up.

In an attempt to make 4-nitrothiophen-3-carbaldehydes we have studied the nitration of a 3-dibromomethylthiophen with blocking groups (Br) at positions 2 and 5. Clarke and Meth-Cohn have shown[1] that 3-methylthiophens can be converted into thiophen-3-carbaldehydes in two states, radical bromination followed by hydrolysis of the 3-dibromomethyl compound using aqueous sodium carbonate. We now confirm that 2,5-dibromo-3-dibromomethylthiophen(1) can be made (in 66% overall yield) from 3-methylthiophen, and we report that although (1) is resistant to aqueous hydrolysis, it can be converted by treatment with ethanolic sodium carbonate to a mixture of the aldehyde and its diethyl acetal, which with aqueous HCl gives 2,5-dibromothiophen-3-carbaldehyde(2) in an overall yield of 95%.[2] The hydrolysis of (1) can also be effected (74% yield) by way of the morpholine aminal and subsequent acid hydrolysis.

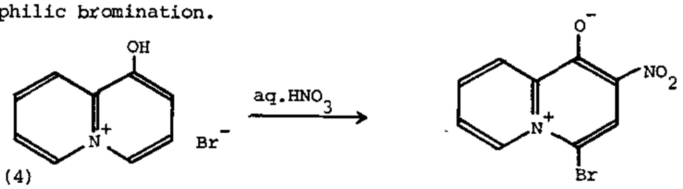


Reaction of (1) with nitric acid in acetic anhydride led to quantitative recovery of the starting material. However, reaction with mixed nitric and sulphuric acids was vigorous in the cold, but after work-up and purification the main product (69%) was found to be 2,4,5-tribromothiophen-3-carbaldehyde(3). The tribromoaldehyde has previously been made[3] by reaction of thiophen-3-carbaldehyde with bromine in thepresence of aluminium trichloride. Compound (3) was also formed, in lower yield (46% crude), by the action of fuming nitric acid (d 1.5) on (1). However, when (1) was treated with either nitric acid or sulphuric acid alone, there was little reaction in the cold, but on warming copious amounts of bromine were evolved. In each case analysis of the crude products immediately after reaction and aqueous work-up showed them to consist largely of the dibromoaldehyde

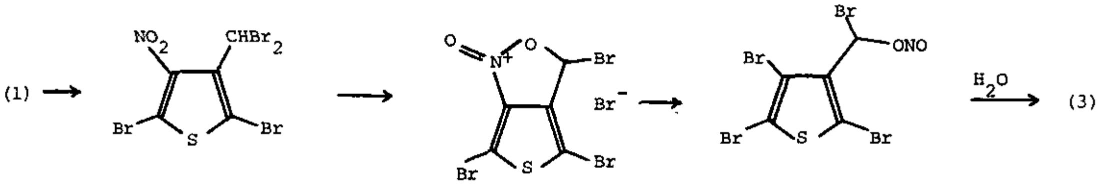
(2), with only small amounts (≤8%) of the tribromoaldehyde(3).

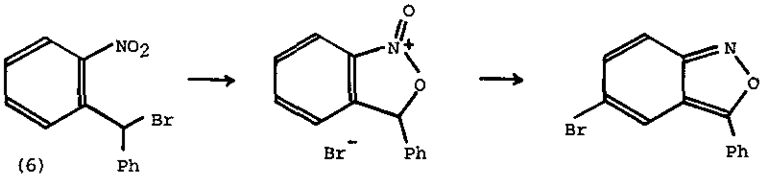


The unusual formation of the tribromaldehyde with mixed acid cannot be attributed to electrophilic bromination of (1) by molecular bromine, since bromine is formed in greater quantities when either acid is used alone. Neither is bromination with a positive species released by ipso substitution a likely mechanism (by analogy[4] with the formation of small amounts of dibromotoluenes in the nitration of 4-bromotoluene), since fairly high yields of (3) are obtained and there is no evidence for any type of nitrated product. The incorporation of bromine during nitration of hydroxy-quinolizinium bromide(4) may offer some analogy,[5] but these salts are known to undergo ready electrophilic bromination.



A plausible mechanism for this unusual reaction involves initial nitration at position 4, followed by ionisation of the dibromomethyl group and then nucleophilic attack by bromide ion to displace the nitro group. The nitro group here plays a vital role both in the initial release of bromide and in further activating the ring to nucleophilic attack. Precedent for this kind of involvement is found[6] in such reactions as that of *o*-nitrobenzhydryl bromide(6).





When the reaction of (1) with mixed acids is carried out in the presence of added sodium chloride, the product is again largely (>90%) the tribromoaldehyde(3), and there is no trace of 2,5-

dibromo-4-chlorothiophen-3-carbaldehyde. This suggests that either the step involving bromide ion attack on the ring occurs within a non-separated ion pair, or full ionisation of the carbon-bromine bond does not take place.

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EXPERIMENTAL

2,5-Dibromo-3-dibromomethylthiophen(1)

Bromine (0.08 mol) in CCl_4 (13 ml) was added over 2 h to a stirred solution of 2,5-dibromo-3-methylthiophen (0.08 mol, prepared from bromine and 3-methylthiophen) and azobisisobutyronitrile (0.04g) in CCl_4 (150 ml) in a flask suspended over a white light source. Further bromine (0.08 mol) and azobisisobutyronitrile (0.4 g) in CCl_4 (13 ml) were added to the refluxing mixture at a rate which maintained the bright yellow colour (4 h). After 1 h of further refluxing, the mixture was cooled, washed with aq. Na_2CO_3, dried (Na_2SO_4) and distilled to give (1). Yield 83%; bp 148-150 ^{o}C/1 mmHg; ir (Nujol): 3010, 1530, 1430, 690 cm^{-1}; δ_H (CCl_4): 6.50 (1H,s) and 7.28 (1H,s)ppm; m/e: 418, 416, 414, 412, 410, 337, 335, 333, 331; found: C,14.65; H,0.50; S,7.82; $C_5H_2Br_4S$ requires : C, 14.51; H,0.49; S,7.75%.

2,5-Dibromothiophen-3-carbaldehyde(2)

(i) A mixture of (1, 0.048 mol), sodium carbonate (0.142 mol), water (50 ml) and ethanol (200 ml) was refluxed for 12 h. After filtration the aqueous layer was extracted twice with ether (50 ml), and the combined organic material was evaporated and filtered. Dilute HCl (50 ml, 1M) was added to the brown oil, and the mixture was refluxed for 1 h. The solution was neutralised with solid Na_2CO_3, the aqueous layer extracted with ether (6 x 25 ml), and the combined organic material was dried (Na_2SO_4) and distilled to give (2) as pale yellow needles. Yield 95%; bp 136 ^{o}C/26 mmHg; mp (40-60 petrol) 48-49 ^{o}C; ir (Nujol): 3100, 1695, 1675, 1175, 1015 cm^{-1}; δ_H (CCl_4): 7.25 (s, 1H) and 9.70 (s, 1H)ppm; m/e: 272, 270, 268 (M^+), 271, 269, 267 $(M-1)^+$; found: C,22.2; H,0.8; Br, 59.2; $C_5H_2Br_2OS$ requires: C,22.2; H,0.7; Br,59.2%.

(ii) A mixture of (1, 0.005 mol) and morpholine (0.03 mol) was heated on a steam bath for 3 h. The product was cooled and then stirred vigorously with crushed ice (20 g), water (50 ml) and hydrochloric acid (10 ml, 36.5%). The solution was neutralised with sodium carbonate, and after extracting with ether, the organic layer was dried (Na_2SO_4), and the solvent removed. Recrystallisation from 40-60 petroleum spirit gave (2) as pale yellow needles (74%). The intermediate morpholine aminal could be isolated by omitting the acid hydrolysis and recrystallising the crude product from ethanol. Yield 81%; mp(d) 146 °C; δ_H (CCl_4): 2.4 (m,8H), 3.6 (m,8H), 3.88 (s,1H) and 6.86 (s,1H); found: C,36.8; H,4.3; N,6.5; $C_{13}H_{18}Br_2N_2O_2S$ requires: C,36.7; H,4.3; N,6.6%.

2,4,5-Tribromothiophen-3-carbaldehyde(3)

Compound (2,0.01 mol) was added in small portions to a stirred mixture of conc. HNO_3 (d 1.42, 3.4 g) and conc. H_2SO_4 (d 1.84, 5.06 g). The dark brown mixture was heated to 60 °C for 1 h and then poured onto crushed ice (30 g). After the mixture was extracted with $CHCl_3$ (6 x 25 ml), the organic layer was dried (Na_2SO_4), and the solvent removed. Recrystallisation from ethanol gave (3) as buff needles. Yield 69%; mp (ether) 100-101 °C; ir (KBr): 1690, 1490, 1060 cm^{-1}; δ_H (acetone-d_6): 9.95 (s)ppm; m/e: 352, 350, 348, 346 (M^+), 351, 349, 347, 345 $(M-1)^+$; found: C,17.3; H,0.3; Br, 68.2; C_5HBr_3OS requires: C,17.2; H,0.3; Br,68.7%. Oxime, mp (ethanol) 188 °C; δ_H (acetone-d_6): 8.05 (s, 1H) and 11.03 (s, 1H)ppm; m/e 367, 365, 363, 361 (M^+); found: N, 3.85; $C_5H_2Br_3NOS$ requires: N, 3.85%.

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